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# Menopausal Complaints Are Associated With Cardiovascular Risk Factors

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**Abstract**—It has been hypothesized that women with vasomotor symptoms differ from those without with respect to cardiovascular risk factors or responses to exogenous hormone therapy. We studied whether the presence and extent of menopausal complaints are associated with cardiovascular risk profile. Data were used from a population-based sample of 5523 women, aged 46 to 57 years, enrolled between 1994 and 1995. Data on menopausal complaints and potential confounders were collected by questionnaires. Total cholesterol, systolic and diastolic blood pressures, and body mass index were measured. Linear and logistic regression analyses were used to analyze the data. Night sweats were reported by 38% and flushing by 39% of women. After multivariate adjustment, women with complaints of flushing had a 0.27-mmol/L (95% CI: 0.15 to 0.39) higher cholesterol level, a 0.60-kg/m<sup>2</sup> (95% CI: 0.35 to 0.84) higher BMI, a 1.59-mm Hg (95% CI: 0.52 to 2.67) higher systolic blood pressure, and a 1.09-mm Hg (95% CI: 0.48 to 1.69) higher diastolic blood pressure compared with asymptomatic women. Flushing was also associated with hypercholesterolemia (odds ratio: 1.52; 95% CI: 1.25 to 1.84) and hypertension (OR: 1.20; 95% CI: 1.07 to 1.34). Results were similar for complaints of night sweating. The findings support the view that menopausal complaints are associated with a less favorable cardiovascular risk profile. These findings substantiate the view that differences in the presence of menopausal symptoms as a reason for using hormone therapy could explain discrepant findings between observational research and trials. (*Hypertension*. 2008;51:1492-1498.)

**Key Words:** menopausal complaints ■ cholesterol ■ blood pressure ■ body mass index  
■ cardiovascular risk profile ■ women

A number of observational studies demonstrated a protective association between hormone therapy (HT) and cardiovascular disease (CVD).<sup>1-3</sup> Placebo-controlled, randomized trials, however, could not confirm a cardioprotective effect and showed no overall benefit of HT on the risk of cardiovascular events.<sup>4,5</sup>

Many potential reasons have been proposed to explain this apparent discrepancy between the observational studies and the trials. An important difference is that, in the observational studies, the most common reason to initiate HT was to relieve menopausal complaints. In contrast, in the trials, women with severe complaints were either excluded or composed only a minority of the total randomized population. Results of a recent subgroup analysis of the combined Women's Health Initiative trials showed that women who initiated HT closer to menopause had a reduced coronary heart disease (CHD) risk compared with the increase in CHD risk among women initiating HT more distant from menopause.<sup>6</sup> Moreover, among women 50 to 59 years old at enrollment in the Women's Health

Initiative, end-of-trial coronary calcium scores were lower in women assigned to estrogens than in those assigned to placebo.<sup>7</sup> A younger age is likely to be accompanied by a higher frequency of menopausal complaints.

We hypothesized previously that women with vasomotor symptoms may differ from those without with respect to cardiovascular risk factors or responses to exogenous HT.<sup>8</sup> Indeed, women with menopausal complaints have a lower level of plasma antioxidant activity and an increased cardiovascular reactivity to stressful situations.<sup>9</sup> In addition, 2 studies demonstrated that hot flushes are associated with an increased blood pressure.<sup>10,11</sup> Moreover, a recent subgroup analysis of the combined Women's Health Initiative trials showed that the higher risks of CHD in women more distant from menopause appeared to be concentrated in the small subset of women with moderate or severe vasomotor symptoms.<sup>6</sup> We examined whether the presence of menopausal complaints is associated with CVD risk profile in a large, community-based sample of perimenopausal women.

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## Subjects and Methods

### Population

The Eindhoven Perimenopausal Osteoporosis Study is a large screening program, established to assess determinants of low bone mineral density in perimenopausal women. The screening of women was carried out between September 1994 and September 1995. The study protocol was approved by 2 institutional review boards, and all of the women provided written informed consent. A detailed description of the study population has been published previously.<sup>12</sup>

The participants eligible for this study consisted of 6700 women, born between 1938 and 1948, aged 46 to 57 years, who took part in the first cross-sectional part of the study. We excluded 1052 women who did not provide information on menopausal symptoms, leaving 5648 women. Another 9 women were excluded because their blood pressure could not be measured, 22 women were excluded because their body mass index (BMI) could not be calculated, and 94 women were excluded because they reported a history of CHD before the baseline measurements, resulting in 5523 women for the analysis. Of the 5648 women for whom we had information concerning complaints, total cholesterol had been measured in a random selected subsample of 2068 women.

### Menopausal Complaints

To assess the frequency of flushing, 3 questions were asked, 1 on the number of days a participant experienced hot flushes in the previous week; 1 on the average frequency of hot flushes at 1 day; and 1 on the highest number of hot flushes at 1 day. Two questions were asked to assess the frequency of night sweats, 1 on the number of nights a participant wakes up in the previous week because of night sweating and 1 on the frequency of waking up per night because of night sweating. From these questions, a dichotomous variable was created for the absence or presence of flushing or night sweats.

Flushing or night sweating was present if a woman reported to have >0 complaints during the previous week or if they answered "yes" on 1 of the questions. In addition, 4 categories of flushing were constructed: absent; having flushes for  $\leq 5$  days per week, with an average of  $\leq 4$  a day, with the highest amount of flushes at 1 day being  $\leq 6$  (low); having flushes for 2 to 7 days per week, with an average of 6 or less a day, and the highest amount of flushes per day being  $\leq 12$  (moderate); and having flushes for >5 days a week, with an average of 3 to 7 a day, with the highest amount of flushes at 1 day being 4 to 30 (high). Moreover, 4 categories of night sweat frequency were constructed: absent; having night sweats for 1 night per week and being awake once (low); having night sweats for more nights per week, but being awake once a night (moderate); and having night sweats for more nights per week and also being awake more than once a night (high).

### Cardiovascular Risk Factors

The cardiovascular risk factors examined in the present study were as follows: (1) total cholesterol levels, (2) hypercholesterolemia, (3) systolic and diastolic blood pressure, (4) hypertension, and (5) BMI. Nonfasting blood samples were taken, and total cholesterol levels were assessed by using an automatic enzymatic procedure<sup>13</sup> at the laboratory of the Diagnostic Center Eindhoven. Hypercholesterolemia was defined as a total cholesterol level  $\geq 6.5$  mmol/L and/or the usage of lipid-lowering drugs.<sup>14</sup> Furthermore, systolic and diastolic blood pressures were measured in a standardized manner using a mercury manometer. One measurement was taken after the participant had been seated quietly in a comfortable posture, with feet flat on the floor, with the back supported and the arm supported at or as close to the level of the heart as possible. Hypertension was classified as a systolic blood pressure  $\geq 140$  mm Hg, and/or a diastolic blood pressure  $\geq 90$  mm Hg, and/or the usage of  $\geq 1$  antihypertensive drug. Weight and height were measured, and BMI was calculated as weight in kilograms divided by height in meters squared.

### Confounders

Women completed questionnaires on education, pregnancies, total duration of oral contraceptive use and HT, drinking of alcohol, smoking behavior, and sport habits. In addition, information was obtained about the use of antihypertensive and cholesterol-lowering therapy (yes or no). Sports activities were classified as yes or no. Smoking was categorized as never, past, or current smoking, and HT use was categorized as current, yes but >3 year ago, and never use. The participants were asked about their education and whether education had been completed. From this information, the highest attained level of education was defined and classified into 4 categories: primary education; lower/intermediate general and lower vocational education; higher general and intermediate vocational education; and higher vocational education and university.<sup>15</sup>

### Data Analysis

All of the statistical analyses were performed using SAS 9.1 (SAS Institute, Inc). Characteristics of the study population are described for all of the women and for women with and without complaints separately by means and SDs for normally distributed continuous variables and numbers and frequencies for categorical variables.

Linear regression analysis was used to analyze the association between the independent variable complaints of flushing or night sweating and the continuous dependent variables cholesterol, systolic and diastolic blood pressure, and BMI. The linear regression coefficients ( $\beta$ ) are presented with 95% CIs. Univariate analysis (model 1) was performed to identify the crude relation between menopausal complaints and cardiovascular risk factors, using the group of women with no complaints as the reference category. In addition, 3 multivariate models were used: model 2, including age; model 3, including smoking, education, sports activities, and HT use; and model 4, incorporating model 3 and BMI.

Because women with menopausal complaints might visit their physician more frequently, and, therefore, have a higher chance of blood pressure being measured and high blood pressure being detected, we repeated the blood pressure analyses in the subgroup of women who did not use antihypertensive drugs. HT is very effective in reducing the menopausal symptoms, and it is likely that women with the worst symptoms would be prescribed HT. Thus, although HT use is strongly linked to the presence of menopausal complaints, the therapy does not cause flushing, but, rather, the opposite is true. Therefore, HT use is a different potential confounding factor than others. For this reason, we repeated all of the analyses in the subgroup of women not using HT.

Logistic regression analysis was performed to examine the relation between menopausal complaints and the presence of hypertension, using the same potential confounders as in the linear regression analyses. *P* values at <0.05 were considered statistically significant.

## Results

In total, 50% reported no symptoms of flushing and night sweats. Flushing only was reported by 12% and night sweats only by 11% of all women, whereas 27% reported having both symptoms. The presence of complaints of night sweating was more common among women with complaints of flushing. The mean age of the study group was  $50.3 \pm 2.4$  years (range: 46.0 to 57.0 years) and was higher in women with complaints. In addition, women with complaints were more likely to be current smokers, current HT users, and to be lower educated than asymptomatic women. In addition, these women were less likely to exercise (Table 1).

### Cholesterol

Women with complaints of flushing had a 0.39-mmol/L (95% CI: 0.27 to 0.50) higher cholesterol level than women without (model 1; Table 2). The difference remained after multivariate adjustment (model 4; Table 2; 0.27 mmol/L; 95% CI:

**Table 1. Characteristics of the Study Population of 5523 Dutch Women According to the Presence of Flushing**

Characteristics	All Women (N=5523)	Presence of Flushing	
		Absent (N=3362)	Present (N=2161)
Age, mean $\pm$ SD, y	50.2 $\pm$ 2.4	49.9 $\pm$ 2.3	50.8 $\pm$ 2.4
BMI, mean $\pm$ SD, kg/m <sup>2</sup>	25.5 $\pm$ 4.4	25.3 $\pm$ 4.3	25.9 $\pm$ 4.5
Systolic blood pressure, mean $\pm$ SD, mm Hg	133.2 $\pm$ 19.4	132.2 $\pm$ 18.9	134.7 $\pm$ 20.1
Diastolic blood pressure, mean $\pm$ SD, mm Hg	83.9 $\pm$ 10.8	83.4 $\pm$ 10.7	84.8 $\pm$ 10.9
Cholesterol, mean $\pm$ SD, mmol/L	6.2 $\pm$ 1.4	6.0 $\pm$ 1.3	6.4 $\pm$ 1.4
Night sweating, % (n)			
Absent	61.9 (3418)	82.1 (2759)	30.5 (659)
Present	38.1 (2105)	17.9 (603)	69.5 (1502)
Hypertension, % (n)			
No	48.8 (2693)	53.7 (1805)	47.4 (1025)
Yes	51.2 (2830)	46.3 (1557)	52.6 (1136)
Hypercholesterolemia, % (n)			
No	63.0 (1303)	67.9 (856)	55.3 (447)
Yes	37.0 (765)	32.1 (404)	44.7 (361)
Sports activities, % (n)			
No	57.2 (3104)	56.0 (1860)	59.1 (1244)
Yes	42.8 (2319)	44.0 (1459)	40.9 (860)
Hormone therapy, % (n)			
Never	77.2 (4224)	80.9 (2698)	71.5 (1526)
Past	3.2 (175)	2.3 (75)	4.7 (100)
Current	19.6 (1072)	16.9 (563)	32.8 (509)
Smoking status, % (n)			
Never	33.8 (1810)	35.4 (1163)	31.3 (647)
Past	32.1 (1718)	32.9 (1080)	30.8 (638)
Current	34.1 (1826)	31.7 (1042)	37.9 (784)
Education completed, % (n)			
Primary	13.7 (738)	11.5 (378)	17.3 (360)
Lower/intermediate general, lower vocational	60.1 (3236)	59.1 (1950)	61.7 (1286)
Higher general, intermediate vocational	13.5 (724)	14.4 (475)	11.9 (249)
Higher vocational, university	12.7 (686)	15.0 (495)	9.2 (191)

Percentages include column percentages.

0.15 to 0.39). Findings were similar for complaints of night sweating. A total of 765 women had hypercholesterolemia (Table 1). After multivariate adjustment (model 4; Table 2), complaints of flushing, as well as night sweating, were associated with an increased prevalence of hypercholesterolemia (odds ratio [OR]: 1.52, 95% CI: 1.25 to 1.84; OR: 1.40, 95% CI: 1.16 to 1.69, respectively).

### Blood Pressure

Adjusted for age (model 2; Table 2), women with complaints of flushing had a 1.46-mm Hg (95% CI: 0.40 to 2.51) higher systolic blood pressure and a 1.03-mm Hg (95% CI: 0.44 to 1.62) higher diastolic blood pressure compared with asymptomatic women. The differences remained after multivariate adjustment (model 3; Table 2; 1.59 mm Hg [95% CI: 0.52 to 2.67] for systolic blood pressure and 1.09 mm Hg [95% CI: 0.48 to 1.69] for diastolic blood pressure). Inclusion of BMI (model 4; Table 2) in the adjustments attenuated the differ-

ences between women with and without complaints but most were still statistically significant (0.81 mm Hg [95% CI: -0.22 to 1.84] and 0.62 mm Hg [95% CI: 0.04 to 1.19], respectively). In total, 2830 women were hypertensive (Table 1). After adjustment for confounders (model 3; Table 2), the presence of flushing was positively associated with hypertension (OR: 1.20; 95% CI: 1.07 to 1.34). When finally adding BMI to the model (model 4; Table 2), the associations were attenuated but still in the same direction with an OR of 1.11 (95% CI: 0.99 to 1.25). In the subgroup of 5074 women who did not use antihypertensive drugs, the associations were somewhat attenuated but were all in the same direction and for night sweats still statistically significant. Results were similar for complaints of night sweating (Table 2).

### Body Mass Index

In the crude analyses (model 1; Table 2) of flushing, women with complaints had a 0.67-kg/m<sup>2</sup> (95% CI: 0.43 to 0.91)

**Table 2. Adjusted Estimates for the Relationship Between Presence of Menopausal Complaints and Cardiovascular Risk Factors in 5523 Dutch Women**

Models	Flushing	Night Sweats
Cholesterol, $\beta$ (95% CI), mmol/L		
Model 1 Present*	0.39 (0.27 to 0.50)	0.32 (0.19 to 0.44)
Model 2 Present†	0.31 (0.19 to 0.43)	0.27 (0.15 to 0.39)
Model 3 Present‡	0.29 (0.17 to 0.41)	0.26 (0.14 to 0.38)
Model 4 Present§	0.27 (0.15 to 0.39)	0.25 (0.13 to 0.37)
Hypercholesterolemia, OR (95% CI)		
Model 1 Present*	1.71 (1.43 to 2.05)	1.48 (1.23 to 1.78)
Model 2 Present†	1.56 (1.30 to 1.88)	1.41 (1.17 to 1.70)
Model 3 Present‡	1.55 (1.28 to 1.87)	1.41 (1.17 to 1.70)
Model 4 Present§	1.52 (1.25 to 1.84)	1.40 (1.16 to 1.69)
Systolic blood pressure, $\beta$ (95% CI), mm Hg		
Model 1 Present*	2.49 (1.45 to 3.54)	2.02 (0.97 to 3.07)
Model 2 Present†	1.46 (0.40 to 2.51)	1.48 (0.43 to 2.52)
Model 3 Present‡	1.59 (0.52 to 2.67)	1.80 (0.74 to 2.87)
Model 4 Present§	0.81 (−0.22 to 1.84)	1.13 (0.11 to 2.14)
Diastolic blood pressure, $\beta$ (95% CI), mm Hg		
Model 1 Present*	1.37 (0.79 to 1.96)	1.10 (0.51 to 1.68)
Model 2 Present†	1.03 (0.44 to 1.62)	0.91 (0.32 to 1.50)
Model 3 Present‡	1.09 (0.48 to 1.69)	1.05 (0.46 to 1.65)
Model 4 Present§	0.62 (0.04 to 1.19)	0.65 (0.08 to 1.21)
Systolic blood pressure in untreated women, $\beta$ (95% CI), mm Hg		
Model 1 Present*	1.92 (0.87 to 2.97)	1.90 (0.85 to .96)
Model 2 Present†	0.90 (−0.16 to 1.96)	1.40 (0.35 to 2.45)
Model 3 Present‡	1.03 (−0.05 to 2.11)	1.71 (0.64 to 2.77)
Model 4 Present§	0.41 (−0.63 to 1.45)	1.20 (0.17 to 2.23)
Diastolic blood pressure in untreated women, $\beta$ (95% CI), mm Hg		
Model 1 Present*	1.25 (0.66 to 1.84)	1.07 (0.47 to 1.67)
Model 2 Present†	0.91 (0.31 to 1.51)	0.90 (0.30 to 1.49)
Model 3 Present‡	0.96 (0.35 to 1.58)	1.02 (0.42 to 1.63)
Model 4 Present§	0.58 (−0.01 to 1.16)	0.71 (0.13 to 1.29)
Hypertension, OR (95% CI)		
Model 1 Present*	1.29 (1.15 to 1.43)	1.26 (1.13 to 1.41)
Model 2 Present†	1.17 (1.05 to 1.31)	1.20 (1.08 to 1.34)
Model 3 Present‡	1.20 (1.07 to 1.34)	1.24 (1.10 to 1.38)
Model 4 Present§	1.11 (0.99 to 1.25)	1.17 (1.04 to 1.31)
BMI, $\beta$ (95% CI), kg/m <sup>2</sup>		
Model 1 Present*	0.67 (0.43 to 0.91)	0.55 (0.31 to 0.79)
Model 2 Present†	0.62 (0.38 to 0.86)	0.51 (0.27 to 0.75)
Model 3 Present‡	0.60 (0.35 to 0.84)	0.51 (0.28 to 0.75)

\*Model 1 indicates univariate (crude) model.

†Model 2 is adjusted for age (continuous).

‡Model 3 is model 2 with smoking (never, past, or current), education (primary, lower/intermediate general, lower vocational, higher general, intermediate vocational, higher vocational, or university), sports activities (yes or no), and hormone use (no; yes, but &gt;3 years ago; or yes).

§Model 4 is model 3 with BMI (continuous).

higher BMI compared with asymptomatic women. Including age and other confounders (model 3; Table 2) in the regression model weakened the results, but women who reporting flushing still had a 0.60-kg/m<sup>2</sup> (95% CI: 0.35 to 0.84) higher BMI. Again, these results were essentially the same for complaints of night sweats (Table 2).

When restricting the analysis to women not using HT, results were essentially similar in this group for all of the outcomes studied, and formal testing using interaction terms was not statistically significant (*P* values ranged from 0.16 to 0.93).

## Discussion

Our data show that women with complaints of flushing or night sweats have an unfavorable cardiovascular risk profile compared with women without vasomotor complaints and with increased cholesterol levels, systolic and diastolic blood pressures, and BMI.

The main strengths of our study are its size and the community-based sampling that improves generalizability of the findings. A limitation is that menopausal symptoms cannot be measured, and we had to rely on self-reported data on complaints. However, assuming that misclassification is nonselective if present, the true relation between vasomotor symptoms and CVD risk profile may be even stronger. For the definition of hypertension, we relied on only 1 blood pressure measurement. Because it has been shown that blood pressure most likely decreases with follow-up visits because of regression to the mean, the prevalence of hypertension in our study may be overestimated.<sup>16</sup> Therefore, these findings should be interpreted with caution. For the continuous measure, it is not as much of a problem. Furthermore, for the analyses of blood pressure, we presented the data for all of the women and additionally for women not treated for hypertension. There are pros and cons for both analyses. Restriction to women without hypertension treatment results in exclusion of women with the highest blood pressures, whereas including them results in underestimation of the true blood pressure of the treated women. The fact that the associations with menopausal complaints in the untreated women are comparable to those including the treated women suggests that blood pressure misclassification in the treated women is not a major issue. This might be because of suboptimal treatment. Finally, the cross-sectional nature of our study makes it difficult to draw conclusions regarding causal pathways.

From the onset of menopause women may experience troubling symptoms that can include vasomotor complaints (hot flushes and night sweats), vaginal dryness, depression, irritability, sleep disturbances, and changes in libido. Evidence from longitudinal studies showed that particularly vasomotor symptoms and vaginal symptoms are causally related to the menopausal transition.<sup>17,18</sup> For the present analyses, we focused on vasomotor symptoms, because data suggest that vaginal and vasomotor symptoms are likely to reflect different pathophysiological processes.<sup>19</sup>

The prevalence of HT use in our study was ≈20%, which is lower compared with the prevalence in countries such as the United States. The higher HT use in the United States could be a consequence of the fact that, in this country, HT was at least in the past more frequently prescribed for the



prevention of chronic diseases. In the Netherlands, however, the main indication for HT use is the presence of menopausal complaints and not preventive purposes.<sup>20</sup> The latter is also consistent with our findings that women with complaints were more likely to be current HT users compared with asymptomatic women.

In previous studies on HT, users tended to be more healthy and health conscious than nonusers.<sup>21</sup> This difference could have led to an overestimation of the beneficial effects and an underestimation of the risks associated with HT use. In our cohort, however, we found that, compared with never users, current users were more likely to be lower educated (72.6% versus 78.1%, respectively) and to have hypertension (50.8% versus 53.3%, respectively) and less likely to be a never-smoker (35.1% versus 29.6%, respectively) and to exercise (56.8% versus 58.4%, respectively). These findings support the view that current users did not have a better cardiovascular risk profile than the never-users and that the healthy user effect probably does not hamper our results.

It is a matter of debate whether it is necessary to adjust for BMI in the analyses regarding blood pressure. In our view, BMI is an important determinant of blood pressure<sup>22,23</sup> and is causally related to endocrine and metabolic changes with menopause, and factors in the causal pathway should not be included in the regression models. The fact that adding BMI to the model attenuated the results supports the view that BMI lies in the causal pathway and that adjustment has led to an overcorrection.

We dichotomized menopausal complaints. However, when complaints of night sweats and flushing were categorized into absent, low, moderate, and high frequency, mean cholesterol, systolic and diastolic blood pressure, and BMI were significantly higher with increasing frequency of complaints (please see the data supplement available online at <http://hyper.ahajournals.org>).

Although vaginal symptoms appear to be more closely related to changes in androgens,<sup>24</sup> vasomotor symptoms are believed to be related to estrogen withdrawal that occurs with the menopause. The latter is supported by the fact that HT is the most successful therapy for reducing their occurrence.<sup>25</sup> However, because there is no significant correlation between plasma hormone levels and the occurrence of vasomotor symptoms,<sup>26</sup> estrogen withdrawal alone cannot fully explain the cause of menopausal symptoms. A growing body of evidence supports the hypothesis that hot flashes result from a reduced thermoneutral zone.<sup>27</sup> This reduction appears to be closely related to increased central nervous levels of norepinephrine (NE), partly through  $\alpha_2$ -adrenergic receptors.<sup>28</sup> The involvement of NE in central thermoregulation and the etiology of hot flashes are supported by results from experimental and animal studies that showed that increased central nervous system levels of NE narrows the width of the thermoneutral zone.<sup>29,30</sup> This is consistent with results from studies that showed that yohimbine, an  $\alpha_2$ -adrenergic antagonist, elevates brain NE<sup>31</sup> and ultimately triggers hot flashes.<sup>32</sup> Thus,  $\alpha_2$ -adrenoceptors in the hypothalamus may be responsible for the events of the hot flash.<sup>28</sup> There is a line of evidence that suggests that the dramatic estrogen variability during the menopausal transition is involved in the etiology

of hot flashes.<sup>33,34</sup> Because estrogens modulate the  $\alpha_2$ -adrenergic receptors,<sup>35</sup> it is possible that the fluctuations in estrogen levels affect the  $\alpha_2$ -adrenergic receptors. A decline in inhibitory presynaptic  $\alpha_2$ -receptors leads to increased NE levels, which leads to inappropriate heat loss mechanisms and an increased occurrence of hot flashes.<sup>28</sup>

The association of menopausal complaints with a more adverse cardiovascular risk profile could result from a primary increase in sympathetic nervous system activity. It has been observed that increased BMI<sup>36</sup> and hypertension<sup>37</sup> are associated with an increased secretion of NE from sympathetic nerves.<sup>38</sup> Activation of the sympathetic nervous system has also been shown to increase the production of serum lipids and lipoproteins by altering lipid metabolic processes,<sup>39</sup> although some studies have found no consistent effect.<sup>40,41</sup> These findings warrant further investigation.

For the present study, we have studied the effects of BMI, lipids, and blood pressure. It has to be acknowledged, however, that time windows of exposure and outcome may vary markedly for different cardiovascular risk factors. BMI and lipids, for instance, most likely reflect effects that have operated over longer periods of time. Blood pressure, however, is a measure that reacts to impulses much quicker. This could be reflected in our findings, because cholesterol and BMI showed the most marked differences, whereas the findings for blood pressure were weaker. It would be interesting to replicate and extend these findings in studies in which other markers of CVD risk are used, such as lipoprotein subfractions, inflammatory markers, etc, and in which CHD events are the outcome.

There are only a few known risk factors for menopausal hot flashes. It has long been thought that women with a higher body weight have a decreased risk for vasomotor symptoms during menopause because of conversion of androgens to estrogens in fat tissue.<sup>42,43</sup> However, these studies are relatively old,<sup>42,43</sup> included very small sample sizes,<sup>43</sup> and used measures for fat mass that are currently considered less appropriate (body weight or percentage ideal weight instead of BMI or fat mass from dual energy x-ray absorptiometry scanning).<sup>42</sup> According to more recent investigations, including our own, women with more body fat are more likely to report hot flashes.<sup>44–46</sup> An explanation might be that increased body fat raises core body temperature,<sup>47</sup> which triggers hot flashes.

Our results show that the presence and frequency of vasomotor menopausal complaints are associated with a more harmful cardiovascular risk profile. These findings lend support to our hypothesis that women with vasomotor symptoms differ from those without with respect to cardiovascular risk factors. These findings substantiate the view that differences in the presence of menopausal symptoms as a reason for using HT could explain discrepant findings between observational research and trials.

## Perspectives

It is beyond dispute that HT is the best remedy for menopausal vasomotor symptoms.<sup>25</sup> Hot flashes are likely to arise as a result of a reduced thermoregulatory zone,<sup>27</sup> which is thought to be primarily caused by a heightened sympathetic

nervous system.<sup>28–30</sup> These alterations in the sympathetic nervous system might be mediated by the estrogen withdrawal associated with menopause.<sup>35</sup> However, estrogen levels stay low throughout menopause, and most hot flush symptoms subside with time. Thus, although a decrease in estrogen concentration could be the first change, it might not directly cause symptoms.<sup>48</sup> It may be speculated that estrogen fluctuations, in addition to a low absolute estrogen levels, are causing the symptoms.<sup>33,34</sup> Moreover, supplementation of HT might increase the absolute estrogen levels in such a way that estrogen fluctuations are not powerful enough anymore to cause symptoms. In the present study we found that vasomotor symptoms are associated with an unfavorable cardiovascular risk profile. Cardiovascular risk factors are also associated with an sympathetic nervous system activity.<sup>36–39</sup> Because a heightened sympathetic nervous system is thought to be involved in the occurrence of menopausal symptoms, as well as in the etiology of the cardiovascular risk profile, it is plausible that the favorable effects of estrogens on the cardiovascular system could derive from the inhibition of the sympathetic nervous system.<sup>49,50</sup> These findings should trigger further research.

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### Disclosures

None.

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